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(54) Substained-release drug preparation.

(57) A sustained-release drug preparation comprises a water-soluble drug, a lipidic substance and an oil as its essential components. The drug level in the blood is sustained at a preferable concentration for a long period of time.

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Sustained-Release Drug Preparation

BACKGROUND OF THE INVENTION

1) Field of the Invention:

This invention relates to a drug preparation which comprises a water-soluble drug, a lipidic substance and an oil as essential components and is suitable for oral administration. When the drug preparation of this invention is administered orally, the velocity of dissolving out the drug in the body is controlled as desired so that the drug level in the blood is maintained at a preferable concentration for a long period of time. The drug preparation of this invention is therefore useful as a pharmaceutical product.

2) Description of the Prior Art:

As means for controlling the duration time of a drug administered orally for therapeutic purposes, various methods have already been proposed including, for example, (i) to disperse a drug in a base insoluble in water such as fat or wax by either dissolving or melting the drug in the base, (ii) to enclose a drug in a physiologically-inert plastic base so that upon its administration, the plastic base remains undigested in the body and is eventually discharged out of the body, and (iii) to disperse a drug in a hydrophilic high-molecular substance so that upon administration, the high-molecular substance is gelled and the drug is gradually dissolved and released from the resultant viscous layer of the thus-gelled high-molecular substance.

Following the above-described conventional techniques, the present inventors conducted a detailed test on the dissolution of effective drug. As a result, the present inventors felt the desire for the provision of a technique which allows to control the velocity of dissolution of a drug as desired by a simple method.

SUMMARY OF THE INVENTION

Based on the above-mentioned finding, the present inventors have carried out an extensive investigation.

As a result of the above investigation, it has been found that the velocity of dissolution of a drug can be controlled by using an oil and a lipidic substance in combination.

In one aspect of this invention, there is thus provided a sustained-release drug preparation comprising as essential components a water-soluble drug, a lipidic substance and an oil.

The sustained-release drug preparation is free of the aforementioned problems of the prior art, namely, has solved the difficulties in the conventional sustained-release means.

BRIEF DESCRIPTION OF THE DRAWINGS

The above and other objects, features and advantages of this invention will become apparent from the following description of the invention and the appended claims, taken in conjunction with the accompanying drawings, in which:

FIGURES 1 - 5 diagrammatically and respectively illustrate the velocities of dissolution of drugs from their drug preparations of this invention in comparison with those of the same drugs from corresponding controls.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

The oral drug in the novel drug preparation of this invention is a water-soluble drug. As its illustrative examples, may be mentioned bunazosin hydrochloride, phenylpropanolamine, chlorphenylamine maleate and theophylline, and the like.

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As exemplary lipidic substances suitable for the formulation of the drug preparation of this invention, may be mentioned aliphatic higher fatty acids such as stearic acid, myristic acid and palmitic acid, and aliphatic higher alcohols such as lauryl alcohol, myristyl alcohol and stearyl alcohol; in addition, esters of higher fatty acids such as the monostearate, distearate and tristearate of glycerin and hydrogenated castor oil, waxes such as bees wax, carnauba wax, Japan wax and whale wax, and hydrocarbons such as paraffin, microcrystalline wax and ceresine; and especially the sucrose esters of fatty acids. They may be used either singly or in combination.

Illustrative of the oil usable in the present invention may include soybean oil, cotton seed oil, sesame oil, peanut oil, olive oil, safflower oil, octyldodecyl glyceride, mignol, glycerin monocaprylate, silicone oil, etc. They may be used either singly or in combination.

In addition to the above-described three essential components, the drug preparation of this invention may also contain, in suitable amount or amounts, one of more desired adjuvants such as those to be described below.

Lactose, crystalline cellulose ("Avicel for Drug and Food Applications", trade name), corn starch, mannitol, talc, silicic acid, calcium stearate, shellac, polyvinyl pyrrolidone, hydroxypropylcellulose, ethylcellulose, calcium carboxymethylcellulose, sodium carboxymethylcellulose, carboxymethylcellulose, hydroxypropylmethylcellulose, etc.

The drug preparation of this invention is obtained by mixing the above-mentioned components at a suitable ratio and then forming the resultant mixture into a preparation form suitable for oral administration such as granules, powder capsules, granule capsules or compression-formed tablets.

As will be shown subsequently by experimental results, the velocity of dissolution of the pharmaceutically-effective component, i.e., the drug from the drug preparation of this invention can be controlled so that its dissolution lasts for many hours.

The drug preparation of this invention will hereinafter be described specifically by the following Examples.

Example 1:

By using components of Table 1 in their respective amounts shown in the same table, three kinds of drug preparations (1), (2) and (3) were separately formulated in the following manner.

In accordance with each of the formulations of the drug preparations (1), (2) and (3) shown in Table 1, bunazosin hydrochloride, "S-370" (trade name, the sucrose ester of a fatty acid) and "Ethocel-10" (trade name) were mixed for 3 minutes in a 20-ℓ super mixer. Then, ethanol was added solely or both octyldodecyl glyceride and ethanol were added in combination. The resultant mixture was kneaded for 3 minutes. The thus-prepared three kinds of masses were separately granulated in a cylindrical granulator equipped with a screen whose openings had a diameter of 0.5 mm. After drying them in a tray dryer, they were separately sifted to 16 - 60 mesh so as to provide the drug preparations (1), (2) and (3).

Table 1

Component mixed \ Drug preparation	(1) (g)	(2) (g)	(3) (g)
Bunazosin hydrochloride	100	100	100
Sucrose ester of fatty acid (S-370)	800	700	600
Ethocel-10 (adjuvant) (ethylcellulose)	100	100	100
Octyldodecyl glyceride	-	100	200
Total	1000	1000	1000

Example 2:

By using components of Table 2 in their respective amounts shown in the same table, two kinds of drug preparations (4) and (5) were separately formulated following the procedure of Example 1 except that the mixing and kneading operations in the super mixer and the granulating operation were each carried out in a state heated at 60 - 70°C.

In the above-described manner, the preparations (4) and (5) were obtained in granular forms.

Table 2

Drug preparation / Component mixed	(4) (g)	(5) (g)
Bunazosin hydrochloride	200	200
Stearic acid	800	750
Sesame oil	-	50
Total	1000	1000

Example 3:

Following the procedure of Example 2, a granular drug preparations (6) and (7) of compositions shown respectively in Table 3 were formulated.

Table 3

Drug preparation / Component mixed	(6) (g)	(7) (g)
Theophylline	400	400
Stearic monoglyceride	600	550
Migriol	-	50
Total	1000	1000

Example 4:

Following the procedure of Example 2, a granular drug preparation (8) of a composition shown in Table 4 was formulated.

Table 4

Drug preparation / Component mixed	(8) (g)
Theophylline	500
Lovely wax (hardened castor oil)	300
Polyvinyl pyrrolidone (K-30)	50
Octyldodecyl glyceride	150
Total	1000

Example 5:

Following the procedure of Example 1, a granular drug preparation (9) of a composition shown in Table 5 was formulated.

Table 5

Drug preparation / Component mixed	(9) (g)
Chlorphenylamine maleate	200
Sucrose ester of fatty acid (S-370)	500
Ethocel-10	50
Silicone oil	200
Total	950

Example 6:

Following the procedure of Example 2, a granular drug preparation (10) of a composition shown in Table 6 was formulated.

Table 6

Component mixed \ Drug preparation	(10) (g)
Phenylpropanolamine	30
Stearyl alcohol	55
Polyvinyl pyrrolidone (K-30)	5
Peanut oil	10
Total	100

The degrees of controlled dissolution of the respective drugs from the corresponding granular drug preparations (1) - (9) were observed in the following manner in accordance with the puddle method. From the respective drug preparations, 100-mg portions were individually collected as samples. Using the second solution of the Japan Pharmacopoeia as a dissolving medium, each of the samples was subjected to dissolution. Their dissolved amounts were determined by comparing their u.v. (λ = 245 nm) absorption data with standard calibration curves which had been prepared from u.v. absorption data obtained by measuring their corresponding drug solutions of prescribed known concentrations, for example, a bunazosin hydrochloride solution (standard solution) prepared separately in advance. The velocities of dissolution from the respective samples, in other words, their dissolution rates along the passage of time, which were obtained in the above-described manner, are shown in FIGURES 1 - 5.

Namely, FIGUREs 1 - 5 diagrammatically show, as a function of time (hours), the rates of dissolution of the drugs from the corresponding drug preparations of this invention into the second solution prescribed in the Japan Pharmacopoeia along with the corresponding data of the samples of the control drug preparations (1), (4) and (6). In each of the drawings, the time of dissolution of the drug is plotted in hours along the axis of abscissas while the percent dissolution is plotted in % along the axis of ordinates. In these drawings, the drug preparation (1) is a control as apparent from Table 1 of Example 1 and did not contain the oil component (octyldodecyl glyceride) among the three essential components in the present invention.

As readily envisaged from FIGURE 1, the percent dissolution reached substantially 100% upon an elapsed time as early as 4 hours in the course of the measurement in the case of the control [the drug preparation (1)]. In contrast, the percent dissolution of the drug preparation (2) finally reached 100% after the lapse of 20 hours of the measurement time. In the case of the drug preparation (3), the percent dissolution was still as little as about 50% even after the lapse of 20 hours of the measurement time.

In addition, it is worthy to note that the drug preparations (2) and (3) have different dissolution curves (i.e., different inclinations) due to the difference in composition in spite of the use of the same components. As suggested by the curves, it is possible to control the velocity of dissolution of a drug as desired by changing the mixing ratio suitably.

FIGURE 2 illustrates a dissolution curve of the drug preparation (4) in which steric acid is incorporated as a sole lipidic substance instead of mixing the oil component among the three essential components in the present invention. Comparing the dissolution curve of the drug preparation (4) with that of the drug preparation (5) which contained all the three essential components of this invention, it is appreciated that the control of the velocity of dissolution of the drug (bunazosin hydrochloride) was considerably improved in the drug preparation (5) owing to the addition of sesame oil in the small amount of 50 g (5%).

FIGURE 3 depicts the velocities of dissolution of the drug, i.e., theophylline contained in the drug preparations (3) and (4) in Example 3. From the dissolution curves, it is possible to have exactly the same analytical observation and understanding as those set forth above with respect to FIGURE 2.

FIGURES 4 and 5 show the velocity of dissolution of the drug preparation (8) in Example 4 and that of the drug preparation (9) in Example 5. The dissolution curves of these drug preparations indicate the achievement of good dissolution control practically similar to the dissolution curves of the above drug preparations (2), (3), (5) and (7).

Having now fully described the invention, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the invention as set forth herein.

Claims

1. A sustained-release drug preparation comprising as essential components a water-soluble drug, a lipidic substance and an oil.

2. The sustained-release drug preparation as claimed in Claim 1, wherein the water-soluble drug is at least one of the drug selected from the group comprising bunazosin hydrochloride, phenylpropanolamine, chlorophenylamine maleate and theophylline.

3. The sustained-release drug preparation as claimed in Claim 1, wherein the lipidic substance is at least one of the substance selected from the group comprising aliphatic higher fatty acids such as stearic acid, myristic acid and palmitic acid, and aliphatic higher alcohols such as lauryl alcohol, myristyl alcohol and stearyl alcohol; esters of higher fatty acids such as the monostearate, distearate and tristearate of glycerin and hydrogenated castor oil, waxes such as bees wax, carnauba wax, Japan wax and whale wax, and hydrocarbons such as paraffin, microcrystalline wax and ceresine; and the sucrose esters of fatty acids.

4. The sustained-release drug preparation as claimed in Claim 1, wherein the oil is at least one of the oil selected from the group comprising soybean oil, cotton seed oil, sesame oil, peanut oil, olive oil, safflower oil, octyldodecyl glyceride, migriol, glycerin monocaprylate, and silicone oil.

5. The sustained-release drug preparation as claimed in Claim 1, wherein the preparation is in the form of a tablet or granules.

Claims for the following contracting states: Austria, Spain and Greece

1. Process for preparing a sustained-release drug preparation comprising mixing as essential components a water-soluble drug, a lipidic substance and an oil.

2. Process as claimed in Claim 1, wherein the water-soluble drug is at least one of the drugs selected from the group comprising bunazosin, hydrochloride, phenylpropanolamine, chlorphenylamine maleate and theophylline.

3. Process as claimed in Claim 1, wherein the lipidic substance is at least one of the substances selected from the group comprising aliphatic higher fatty acids such as stearic acid, myristic acid and palmitic acid, and aliphatic higher alcohols such as lauryl alcohol, myristyl alcohol and stearyl alcohol; esters of higher fatty acids such as the monostearate, distearate and tristearate of glycerin and hydrogenated castor oil, waxes such as bees wax, carnauba wax, Japan wax and whale wax, and hydrocarbons such as paraffin, microcrystalline wax and ceresine; and the sucrose esters of fatty acids.

4. Process as claimed in Claim 1, wherein the oil is at least one of the oils selected from the group comprising soybean oil, cotton seed oil, sesame oil, peanut oil, olive oil, safflower oil, octyldodecyl glyceride, migriol, glycerin monocaprylate, and silicone oil.

5. Process as claimed in Claim 1, wherein the preparation is additionally made into the form of a tablet or granules.

Fig. 1

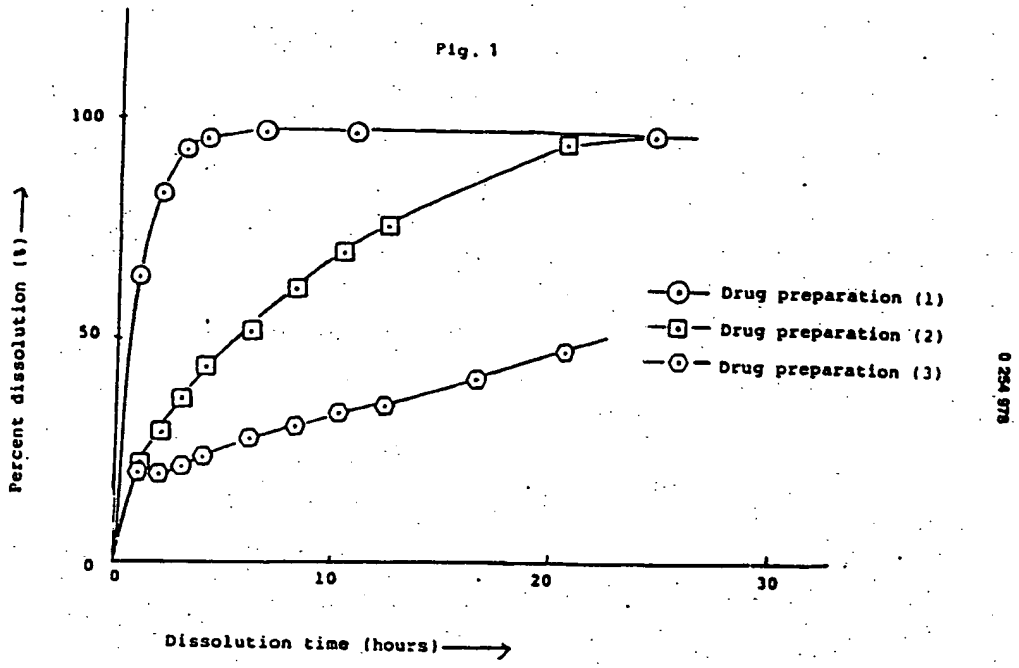

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Fig. 2

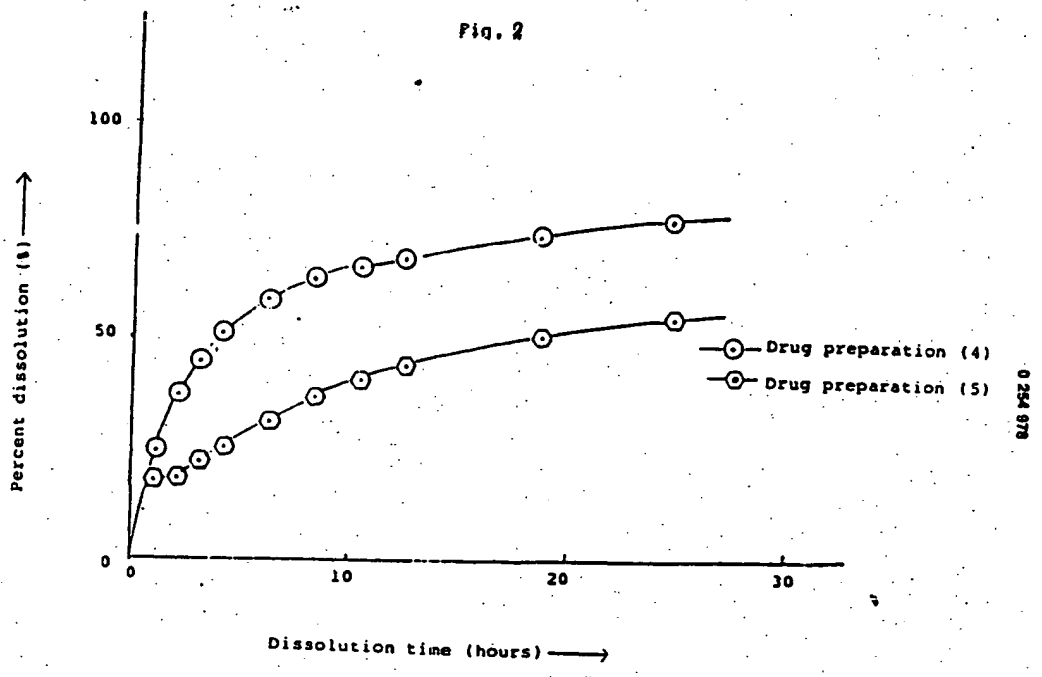

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Fig. 3

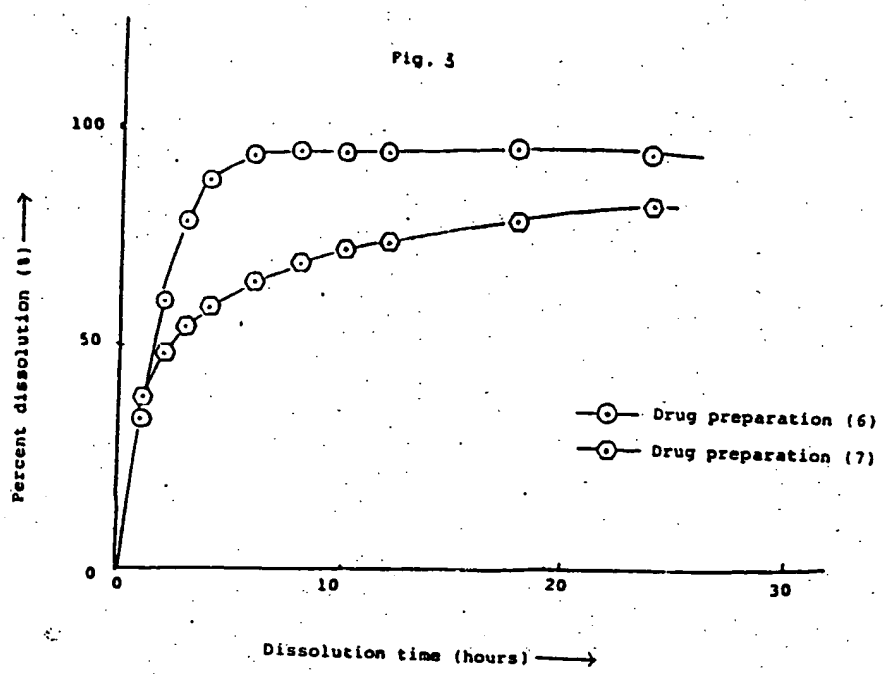

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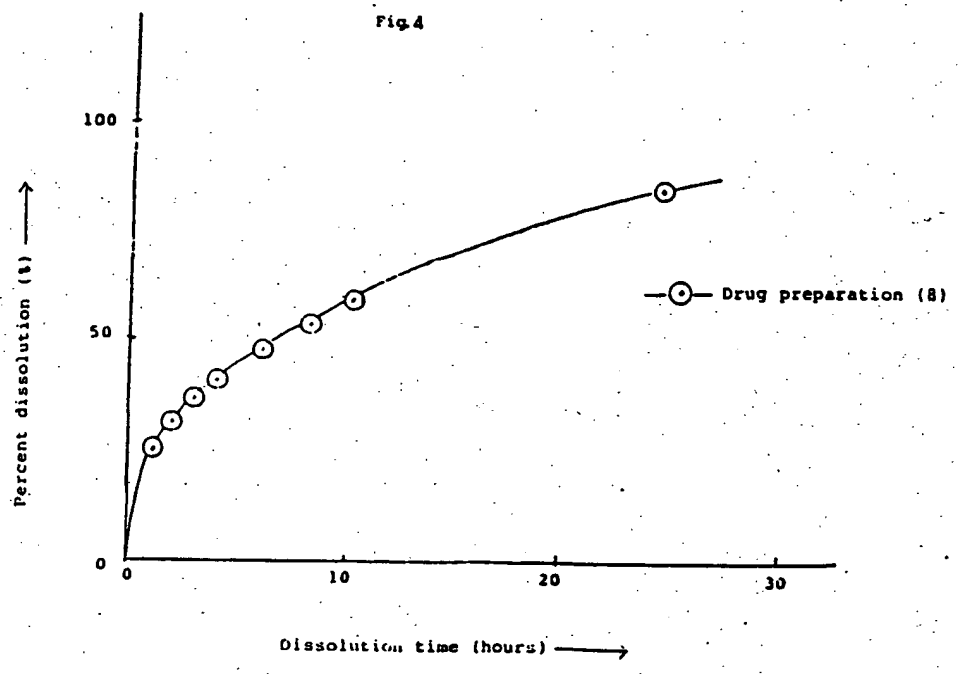
Fig.4



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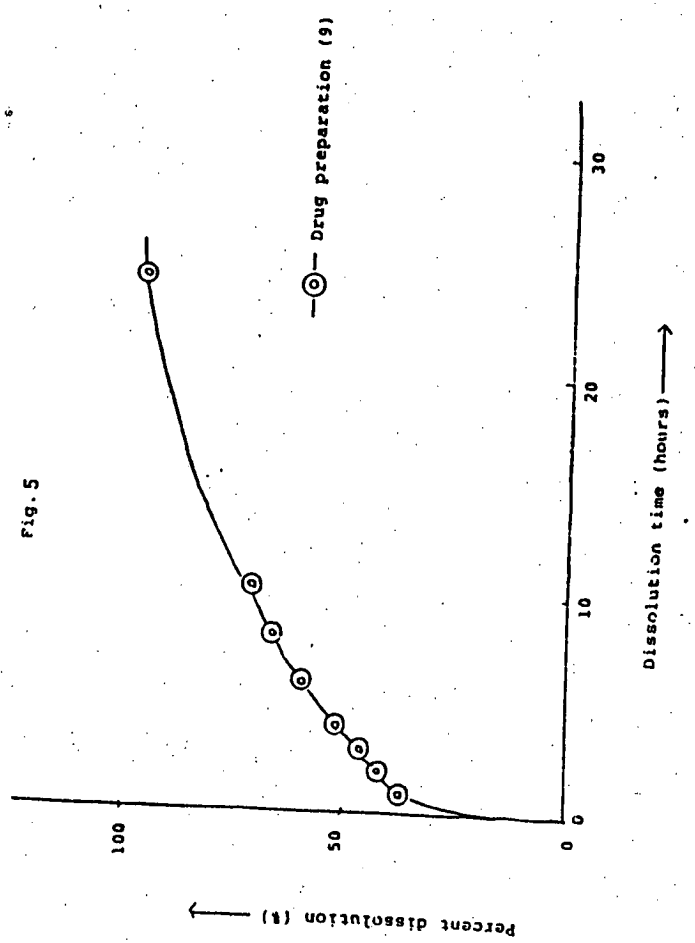

Fig.5

European Patent Office

EUROPEAN SEARCH REPORT

Application number

EP 87 11 0297

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int Cl 4)
X	EP-A-0 176 772 (RODISMA PHARMEZEUTISCHE PRODUKTE GmbH) * Page 10, lines 28-34; pages 11-13; formulations; examples 1,8 *	1,3,4	A 61 K 9/22 A 61 K 47/00
Y		2,5	
X	US-A-3 655 864 (G.M. GRASS) * Abstract; column 3, table I, examples 5,6; column 5, lines 15-20,40-45,56-62; column 4, lines 59-73 *	1,3-5	
Y	GB-A-2 163 648 (NIPPON SHINYAKO CO. LTD) * Page 1, line 61; page 2, line 61 - page 3, line 43; page 5, example 4 *	2,5	
A	US-A-4 020 159 (J.P. HERRMANN) * Column 2, lines 1-16; columns 11-13, claims 1,5-8 *	1-5	TECHNICAL FIELDS SEARCHED (Int Cl 4) A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	26-10-1987	FOERSTER W.K.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
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